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Dkt. 50875-F-PCT-US/JPW/MAF

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant : Graham P. Allaway, et al.  
U.S. Serial No.: 09/460,216 Examiner: J. Parkin  
Filed : December 13, 1999 Group Art Unit: 1648  
For : METHODS FOR PREVENTING HIV-1 INFECTION OF  
CD4+ CELLS  
1185 Avenue of the Americas  
New York, New York 10036

Assistant Commissioner for Patents  
Washington, D.C. 20231

SIR:

**DECLARATION UNDER 37 C.F.R. §1.132 OF TATJANA DRAGIC**

I, Tatjana Dragic, Ph.D., hereby declare that:

1. I am employed by Albert Einstein College of Medicine, Bronx, New York as an Assistant Professor of Microbiology and Immunology. I received a Ph.D. degree in Molecular and Cellular Biology from the University of Paris and I have 13 years of experience in the field of HIV research. A copy of my curriculum vitae is attached hereto as Exhibit 1.
2. I am married to Dr. Paul J. Maddon, who is a coinventor on the above-identified patent application, and who is the Chief Executive Officer of Progenics Pharmaceuticals, Inc., the assignee of the above-identified patent application.
3. I have read and am familiar with the specification and claims of the above-identified application.

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4. I understand the claimed invention to be a method of inhibiting HIV-1 infection of a CD4+ cell, wherein the method comprises contacting a CD4+ cell with a nonpeptidyl agent capable of binding to a CCR5 chemokine receptor in an amount and under conditions such that fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell is inhibited, so as to thereby inhibit HIV-1 infection of the CD4+ cell.
5. I understand that a patent for the claimed invention has been rejected by the United States Patent and Trademark Office for allegedly not being enabled by the application's specification.
6. I and my colleagues in the field of research involving the human immunodeficiency virus ("HIV") knew of the Resonance Energy Transfer ("RET") assay and the use the RET assay to screen for compositions having an effect on HIV-1 or HIV-1 infected cell-CD4+ fusion. The assay was well known by those skilled in the field as of April 2, 1996. Evidence of such knowledge includes PCT International Publication No. WO 95/16789 entitled, "Methods For Using Resonance Energy Transfer-Based Assay of HIV-1 Envelope Glycoprotein-Mediated Membrane Fusion, and Kits For Practicing Same", published June 22, 1995. A copy of WO 95/16789 is attached hereto as Exhibit 2.
7. Based on the patent application (as discussed below in ¶¶9-13) and the general knowledge in the field concerning the use of Resonance Energy Transfer assays as of April 2, 1996, as evidenced by Exhibit 2 (noted

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in ¶6 above), one skilled in the art could readily, without the need for any significant, i.e., undue, amount of experimentation, have utilized such RET assays for determining whether any given nonpeptidyl agent is capable of inhibiting, and using such agent to inhibit, the fusion of HIV-1 or an HIV-1 infected cell to a CD4+ cell.

8. As of April 2, 1996 the level of ordinary skill in the art of utilizing such RET assays for measuring cell fusion between a CD4+ cell and HIV-1 or an HIV-1 infected cell was a master's degree or higher in cell biology or a related field and at least one year of experience. Such a person of ordinary skill, using an RET assay, could have readily determined, without the need for any significant or undue amount of experimentation, the inhibition of fusion between HIV-1 or an HIV-1 infected cell and a CD4+ cell having a CCR5 chemokine receptor, as recited in the present invention, as of April 2, 1996. In summary, the invention as taught in the present specification may be readily practiced by one of ordinary skill in this art with the use of the well-understood, as of the time of the invention, RET screening technique for determining specific nonpeptidyl agents which will inhibit fusion between a CD4+ cell and HIV-1 or an HIV-1 infected cell.
9. The present application provides substantial disclosure, and thus a significant degree of guidance, as to the use of RET assays for determining the presence of cell fusion, which assays are, as noted above, well-understood, and which provide reliable,

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reproducible results which are readily capable of being practiced by one of ordinary skill. The application teaches, at p.1, line 32 to p.2, line 2, that a RET assay offers a significant advantage in the art in determining whether compounds including chemokines differentially inhibit fusion mediated by the envelope glycoprotein from the primary macrophage-tropic isolate of HIV-1<sub>JR-FLT</sub> in comparison to fusion mediated by the envelope glycoprotein from the laboratory adapted T lymphotropic strain HIV-1<sub>LAI</sub>.

10. The specification goes on to disclose, at p.3, lines 1-7, the use of an RET assay for identifying non-chemokines which, according to the teaching of the application, include non-peptidyl agents (see ¶12 below), that inhibit HIV-1 envelope glycoprotein mediated membrane fusion and which thereby neutralize the HIV-1 virus without producing an inflammatory response.
11. The specification of the application further provides, at p.5, line 28 to p.6, line 7, a description of the RET assay for use in determining, in accordance with the claimed invention, whether any given non-chemokine agent inhibits the fusion of HIV-1 to a CD4+ cell.
12. More specifically, the specification discloses, at p.19, line 22, a particular RET assay methodology for determining whether a non-chemokine agent is capable of inhibiting the fusion of HIV-1 to a CD4+ cell. Such non-chemokine agents are defined, on p.20, lines 26-27, to include nonpeptidyl agents. These agents are specifically useful in the invention claimed in the

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present application.

13. The Experimental Details section of the application's specification teaches (see, in particular, pages 26 and 34), the use of RET assays for testing the effect of a variety of materials with the aim of using such materials to prevent fusion between HIV-1 or HIV-1 infected cells and CD4+ cells. Table 2 on p.35 of the specification provides a summary of the effect of  $\beta$ -chemokines on HIV-1 envelope glycoprotein-mediated membrane fusion, as measured using an RET assay. See also, p.40, lines 25-34 of the specification discussing an RET assay of the fusion capacity of  $\beta$ -chemokine receptors. More particularly the specification provides a working example, in the Fourth series of Experiments (in the paragraph bridging pp.45-46 of the text) of the use of a specific nonpeptidyl agent, i.e., the bicyclam, JM 3100, for inhibiting HIV-1 envelope-mediated membrane fusion. The specification states, with regard to this nonpeptidyl agent that, as illustrated in Fig. 7 of the application, JM 3100 specifically and potently inhibits fusion mediated by gp120/gp41 from the HIV-1<sub>LAI</sub> strain, but not from the HIV-1<sub>JR-FL</sub> strain (p.46, lines 7-10). Thus the specification provides substantial guidance in practicing the claimed method of the invention to one of ordinary skill in this art.

14. It is not necessary for one of ordinary skill in this art, searching for nonpeptidyl agents which will bind to a CCR5 chemokine receptor located on a CD4+ cell so as to inhibit fusion between HIV-1 or an HIV-1

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infected cell and a CD4+ cell, to know in advance the structure of the agent. This is clearly demonstrated by the disclosure contained in the Abstract of Olson, et al., "Identification of CCR5 Coreceptor Inhibitors That Potently and Selectively Block HIV-1 Replication" (the Olson, et al. Abstract). I am a co-author of this Abstract and a copy is attached hereto as Exhibit 3. This Abstract was presented at the 9<sup>th</sup> Conference on Retroviruses and Opportunistic Infection held in Seattle, Washington from February 24 to February 28, 2002.

15. The Olson, et al. Abstract provides data which demonstrates that using the RET method of screening, as disclosed in the specification of the present application, nonpeptidyl compounds were identified that are useful in the claimed invention (see ¶4 above) without prior knowledge of the structure of these nonpeptidyl compounds and without the need for any significant, i.e., undue, amount of experimentation. As set forth in the Olson, et al. Abstract, following high throughput screening of a chemical compound library, a cell-based RET assay identified multiple active compounds. The compounds, and analogs thereof, identified as inhibiting fusion between CD4+ cells and HIV-1 or HIV-1 infected cells from the RET assay, were further characterized using secondary assays (see ¶16 below). The Olson et al. Abstract thus discloses that without advance knowledge of the structure of the compounds that specifically block CCR5-mediated, but not CXCR4-mediated HIV-1 cell-cell and virus-cell-fusion, compositions, including nonpeptidyl compounds, were readily defined

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without the necessity for any significant amount of experimentation.

16. The secondary assays, mentioned in ¶15 above, are described in the Olson, et al. Abstract, as employing a series of env-complemented luciferase reporter viruses (as well as primary HIV-1 isolates). These assays are discussed in detail at, for example, pp.31-34 of the present application. The results of the use of these assays are summarized at Table 1 p.32 and Table 3 at P. 37 of the specification. This disclosure thus clearly established that luciferase assays as in the Olson, et al. Abstract, were also well understood by one of ordinary skill in the art at least as of the filing date of the present application.
17. In summary, even without prior knowledge of the structure of the compounds sought, but with knowledge of their desired use, one of ordinary skill in the art at the time the invention was made would be readily able, relying upon the detailed teachings or guidance concerning the RET assay provided in the present specification, determine without undue experimentation appropriate nonpeptidyl agents useful in the claimed method, which claim is clearly commensurate in scope with the disclosure of the invention as taught in the specification of the application.
18. It is my expectation and belief that nonpeptidyl compounds and analogs thereof that bind the CCR5 chemokine receptor of CD4+ cells and inhibit fusion of HIV-1 or HIV-1 infected cells as determined by the RET assay have reasonable probability to inhibit and treat

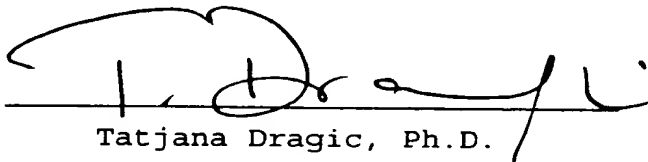
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HIV-1 infection in humans.

19. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like ~~so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may~~ jeopardize the validity of the application or any patent issued thereon.

Date:

3/31/02

  
Tatjana Dragic, Ph.D.